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## APLASTIC ANAEMIA DUE TO PHENYLBUTAZONE

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IT HAS been estimated (Annotation, 1962) that in any given week in Great Britain alone, 100,000 people are taking phenylbutazone. There are several well known side effects from this drug, and a considerable number of cases in which marrow depression has occurred have already been reported (Leonard, 1953; Kersley and Mandell, 1963; Kaplin, 1955; Venning, 1957; Hale and DeGruchy, 1960; Rankin, 1961; Lander and Bonnin, 1962; McCarthy and Chalmers, 1964; Humble, 1964; Woodliff and Dougan, 1964). Our search of the literature has revealed 15 cases of aplastic anaemia in patients taking phenylbutazone; in 7 of these cases the marrow failure proved fatal.

We record the following case of fatal aplastic anaemia because it re-emphasises the possible dangers of this drug and the need for extreme wariness when it is being used.

### Case Report

A 79-year-old widow was admitted to hospital on the 6th of November, 1964. Pernicious anaemia had been diagnosed in 1954 and had been well controlled with cytamene given every three weeks. About the end of 1963 she had complained of "arthritic pains" in the hands and legs, and her own doctor prescribed phenylbutazone, 100 mg. tablets, one thrice daily. In fact she took the tablets rather erratically, so that the total amount taken over a period of 11 months was approximately 10 g. (about 100 tablets). Three weeks prior to admission spontaneous bruises appeared on the right arm, and shortly after she noticed what transpired to be a typical purpuric rash on both lower limbs. Phenylbutazone was stopped on October 14th, 1964.

On admission she was well nourished, rather obese and obviously anaemic, but not jaundiced or cyanosed. The tongue was covered with small

purpuric lesions, also noted in other parts of the buccal cavity. There was a one centimetre bruise on the lower lip, which was superficially infected. There was no lymphadenopathy. Pulse regular, 100/min., normal volume; the blood pressure was 130/80 mm. Hg. JVP not raised; no sacral or ankle oedema. The heart was not clinically enlarged and heart sounds were normal. The liver and spleen were impalpable. The central nervous system was normal. In the right fundus there were haemorrhages around the disc margin; the left fundus was normal. There was no evidence of peripheral neuropathy or of lateral column involvement as might have occurred in association with her known pernicious anaemia.

*Initial Investigations:* Hb. 5.6 g./100 ml., RBC 2,000,000/cu. mm. (retics 0.2%), PCV 19%, MCHC 31%, ESR 136 mm./1 hour, WBC 2,100/cu. mm. (Polys. 8%, Lymphs. 90%, Lymphoblasts 1%, Monos. 1%). Platelets 45,000/cu. mm. Bleeding Time (McFarlane) 24 min., Clotting Time (Capillary) 4½ min., Prothrombin Activity (Thrombo Test) 100% of average normal, Direct Coombs Test negative, Serum Iron 157 µg./100 ml. Blood Group 'A' positive.

*Blood film:* The blood film showed normal erythrocytes with occasional late normoblasts; an occasional primitive leucocyte was present and agranulocytosis was obvious. Platelets were very sparse.

*Sternal Marrow:* Sections of the marrow showed 95% fat with only an occasional island of haemopoietic tissue (Fig. 1a & b). These islands were mainly lymphocytes and showed no polymorphonuclear cells or megakaryocytes. Differential count showed a leuco-erythroid ratio of 5 to 1. The leucopoietic tissue was 75% lymphocytes with a few lymphoblasts. Primitive cells were not frequent. Erythropoiesis was normoblastic with no arrest of maturation. The overall picture was that of aplasia, affecting most severely thrombocytes and granulocytes; to a slightly less degree the erythrocytes.

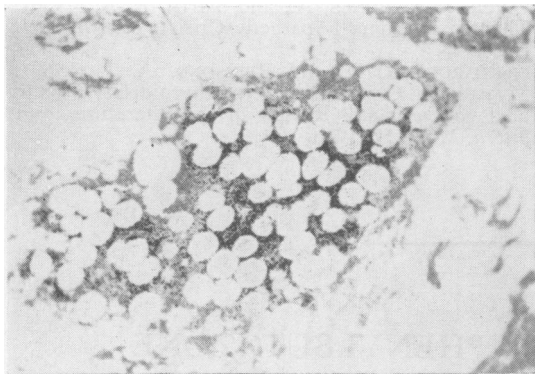


FIG. 1 (a)—Sternal marrow section (H. & E. x 4.4). The marrow is largely replaced by fat.

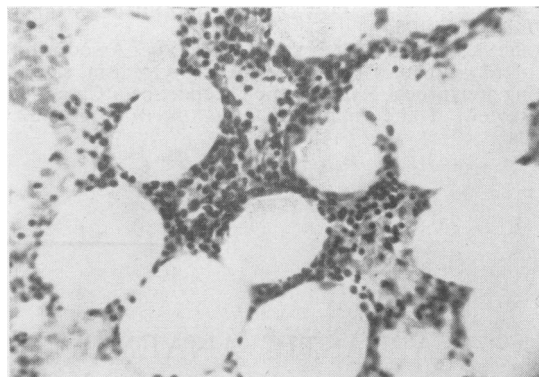


FIG. 1 (b)—Same section (x18).

Serum sodium 134, potassium 4.1, chloride 96, bicarbonate 22.4 mEq./l.

Serum alkaline phosphatase 13.0 K.A. units, bilirubin (direct) negative, (total) 0.8 mg.%, thymol turbidity 4 units, thymol flocculation negative, zinc sulphate turbidity 7 units, total serum proteins 6.3 g.%, albumin 3.6 g.%, globulin 2.7 g.%, S.G.O.T. 40 S.F. units, S.G.P.T. 52 S.F. units.

**Clinical Course:** Two pints of whole fresh blood and packed cells from two pints of fresh blood were transfused shortly after admission. Phenoxymethyl penicillin was started, 500 mg. q.d.s. for three days, followed by 250 mg. q.d.s. Prednisone was started at once, 60 mg. daily. Initially there was quite marked subjective improvement, but bruising increased in the buccal cavity. The platelet count rose to 90,000/cu. mm. On the seventh day, further transfusion was given because the haemoglobin was still only 7.7 g./100 ml. Despite further transfusion to a total of 12 pints haemoglobin and platelet counts steadily dropped, and on the tenth day from admission she became comatose, and died a few hours later. The immediate cause of death was thought to be brain stem haemorrhage.

**Necropsy:** Death was due to multiple haemorrhages resulting from thrombocytopenia. Externally there were extensive petechiae over the arms and legs, and a large ecchymosis on the lower lip. The meninges showed extensive subdural haemorrhages up to 5 mm. in thickness, covering the whole of the vault and base of the skull. There was evident pulmonary oedema. The heart was of normal size, and coronary arteries normal. The stomach contained approximately 200 ml. of fresh blood but was otherwise normal. The small intestine was distended with blood but the large intestine was normal. The spleen was of normal size and architecture; both adrenals were normal; the kidneys were pale and the pelvis filled with fresh blood. The bladder contained bloodstained urine.

### Discussion

Leonard (1953) has summarised some of the non-haematological complications associated with phenylbutazone. Sodium and water retention may cause oedema and precipitate cardiac failure. Nausea, vomiting and diarrhoea are common but not serious; of more importance is possible re-

activation of peptic ulcer, which may result in haematemesis and melaena. Skin rashes have occurred frequently, and jaundice rarely.

Mauer (1955) and more recently McCarthy and Chalmers (1964) have given excellent reviews of the haematological complications of phenylbutazone therapy, and to date there have been some 85 cases of such complications published in the English literature. These are summarised in the table, in which the present case has been added, making the total cases 86, of which 20 have been fatal. We have added our case because it seems an inescapable conclusion in view of the evidence presented that the marrow failure was due to phenylbutazone.

It is possible that the dose of phenylbutazone may bear little relationship to the development of haematological complications in any given case. In the present instance the estimated total was 10g. In the other reported cases the lowest total dose was 4g., the highest 300g. Moreover, intermittent therapy may be just as dangerous, possibly due to a sensitisation mechanism in the marrow (Kersley and Mandell, 1953).

We have been able to trace only one other example of aplastic anaemia, apparently due to phenylbutazone, in a patient proved to have pernicious anaemia (Lander and Bonnin, 1962). This was the case of an elderly woman, who had taken phenylbutazone for nine months, and who

TABLE 1.

| Complication                                    | No. of Cases | Deaths |
|-------------------------------------------------|--------------|--------|
| Agranulocytosis                                 | 37           | 11     |
| Thrombocytopenia                                | 31           | 1      |
| Aplastic Anaemia*                               | 16           | 8      |
| Megaloblastic Anaemia<br>(Folic Acid Dependent) | 1            | 0      |
| Depression of<br>Erythropoiesis                 | 1            | 0      |
| TOTAL                                           | 86           | 20     |

\*Including present report.

presented with megaloblastic anaemia, histamine fast achlorhydria, gastric atrophy, and low serum B<sub>12</sub> levels. On treatment with vitamin B<sub>12</sub> the marrow became normoblastic, but there was no peripheral reticulocytosis; and she died two months later from aplastic anaemia. These authors suggested that underlying aplasia had prevented the anticipated response to vitamin B<sub>12</sub>.

So far as we are aware aplastic anaemia has not been reported as a complication of true pernicious anaemia *per se*.

Wright (1963) has pointed out that it is doubtful if phenylbutazone has specific anti-rheumatic properties, and that its main effect is analgesic. Moreover, he claims that no adequate clinical trials have been carried out to compare the analgesic properties of phenylbutazone and aspirin.

It is apparent that whenever phenylbutazone is employed, the patient should be kept under very close clinical and haematological review.

### Summary

A case of aplastic anaemia occurring in an elderly woman who had taken 10g. of phenylbutazone over a period of 11 months is reported. The patient was known to have had pernicious anaemia for ten years. The haematological complications of phenylbutazone are briefly reviewed. It is important that any patient receiving phenylbutazone be kept under close haematological review, and the drug be stopped at once should suspicion of selective or general marrow depression arise.

So far as we are aware, however, even such

early detection and immediate suspension of the drug may not alter the prognosis in any given case.

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## ACUTE MYELOBLASTIC LEUKAEMIA PRESENTING WITH ERYTHEMA NODOSUM

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ERYTHEMA nodosum associated with leukemia is rare although a few cases have been described. The common cutaneous manifestations are petechial haemorrhages, purpuric spots, prurigo-like papules resembling dermatitis herpetiformis, exfoliative dermatitis, and occasionally erythema multiforme. The association of erythema nodosum has been reported with acute monocytic leukemia, (Bluefarb, 1960; Lynch, 1936), with chronic

lymphatic leukemia (Gate and Cuilleret, 1937); with aleukemic leukemia (Kourilsky, Beauvy and Anglade, 1937); and chronic granulocytic leukemia (Piacentini, 1956; Wintrobe and Mitchell, 1940). Recently a case of erythema nodosum as an initial manifestation of acute stem cell leukemia was published (Pinski and Stansifer, 1964), but there is no published report as yet of its association with acute myeloblastic leukemia. The following case report describes a patient who presented with erythema nodosum and was found to have acute myeloblastic leukemia.

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